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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,422	11/07/2006	Eggert Stockfleth	50125/084002	7550
21559	7590	05/17/2010		
CLARK & ELBING LLP			EXAMINER	
101 FEDERAL STREET			MI, QIUWEN	
BOSTON, MA 02110			ART UNIT	PAPER NUMBER
			1655	
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			05/17/2010	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

[patentadministrator@clarkelbing.com](mailto:patentadministrator@clarkelbing.com)

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/574,422	STOCKFLETH, EGGERT	
	<b>Examiner</b>	<b>Art Unit</b>	
	QIUWEN MI	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 22 March 2010.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,4-6,8-28 and 30-36 is/are pending in the application.  
 4a) Of the above claim(s) 33 and 34 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1,4-6,8-28,30-32,35 and 36 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>3/22/2010</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
|  | 6) <input type="checkbox"/> Other: _____ .                        |

## DETAILED ACTION

Applicant's reply filed on 3/22/2010 is acknowledged, with the cancellation of Claims 2, 3, 7, and 29. Claims 1, 4-6, 8-28, and 30-36 are pending. Claims 33 and 34 are withdrawn.

### **Claims 1, 4-6, 8-28, 30-32, 35, and 36 are examined on the merits.**

Any rejection that is not reiterated is hereby withdrawn.

### **Double Patenting Rejection**

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 8-28, 30-32, and 36 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 16, 18, 23-27, and 30-33 of copending Application No. 10/682, 612. Although the conflicting claims are not identical, they are not patentably distinct from each other because actinic keratosis in case 10/682,612 is a species of the broad genus "pre-cancerous lesions" in the instant case, thus claims 1-6, 8, 16, 18, 23-27, and 30-33 of copending Application No. 10/682, 612 'anticipate' the Claims 1, 6, 8-28, 30-32, and 36 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### **Claim Rejections –35 USC § 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-5, 8-15, and 35 are newly rejected under 35 USC § 102 (b) as being anticipated by Lou et al (Lou et al, Effects of topical applications of caffeine or (-) epigallocatechin gallate (EGCG) on skin carcinogenesis and apoptosis in SKH-1 hairless mice previously treated with ultraviolet B light (high risk mice), Proceedings of the American Association for Cancer Research, 43: 1143, 2002, March).

Lou et al teach in earlier studies, we report that oral administration of green tea, inhibited the formation and growth of skin tumors in high risk mice previously treated with ultraviolet B light UVB). In the present study, female SKH-1 mice (thus a patient) were irradiated with UVB (30 mj/cm<sup>2</sup>) (thus non-virally induced, thus the lesion is not caused by papilloma virus) twice weekly for 20 weeks, and UVB administration was stopped. Three weeks later, these tumor-free high risk mice were treated topically with EGCG (thus a polyphenol isolated and extracted from green tea, thus the same as epigallocatechol gallate, thus the limitations of claims 12-15 are met)

(3.0 mg, 6.5  $\mu$ mol) in 100  $\mu$ l acetone once a day, 5 days a week for 18 weeks. Topical applications of EGCG to these mice decreased the number of tumors per mouse by 56%, and the average tumor volume per mouse was decreased by 23%. Immunohistochemical analysis of 10 squamous cell papillomas, 411 keratoacanthomas (thus a precancerous lesion, thus a type of acanthoma, thus the limitation of claim 35 is met, thus the lesion is not hyperplasia, condyloma acuminate, warts, or cervical intra-epithelial neoplasia) and 55 squamous cell carcinomas that were characterized by histopathological examination showed that topical applications of EGCG increased the number of caspase 3 positive cells in keratoacanthomas (nonmalignant tumors) by 73%, and caspase 3 positive cells in squamous cell carcinomas were increased by 56%. Topical applications of EGCG had little or no effect on apoptosis in non-tumor areas of epidermis. The effect of topical applications of EGCG on tumor cell proliferation, assayed by BrdU incorporation into DNA, are currently being evaluated. The results of these studies suggest further research to determine possible topical effects of EGCG on sunlight-induced skin cancer in humans (see the entire document).

Therefore, the reference is deemed to anticipate the instant claim above.

### **Claim Rejections –35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 4-6, 8-15, 27, 28, 30-32, and 35 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Lou et al as applied to claims 1, 4-5, 8-15, and 35 above, and further in view of Brash et al (US 2002/0198161), and further in view of Voet (US 6,723,750).

The teachings of Lou et al are set forth above and applied as before.

The teachings of Lou et al do not specifically teach additive isopropyl myristate, form of ointment, or combined with different treatment curettage to treat human patient

Brash et al teaches that skin precancers are being treated, the preferred mode of administration is topical. The topical application may contain carrier, excipient or vehicle ingredients such as isopropyl myristate etc., and mixtures thereof to form lotions, creams, emulsions, gels, or ointments [0086]. Brash et al also teaches a method of preventing a precancer, cancer, hyperproliferative or benign dysproliferative disorder in a human subject (claim 76).

Voet teaches that the current management options for visible or easily perceived and diagnosed precancerous dermatological lesions such as Aks (thus claim 35 is met) include cryosurgery with liquid nitrogen, topical treatment, and curettage (col 2, lines 15-20). Voet also teaches that curettage, which involves the use of a curette to scrape away the lesion, is another common method of treatment for easily perceptible precancerous skin lesions. The primary advantage of curettage is the ability to submit the specimen for histologic analysis.

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the carrier isopropyl myristate and ointment form for human subject from Brash et al, and the treatment of curettage from Voet in the current invention

since carrier isopropyl myristate and ointment form are the conventional carrier and pharmaceutical form that have been used successfully in treating precancerous lesions in the topical route according to Brash et al; and combining the treatment curettage from Voet with the topical could monitor the histologic status of the tissue treated by topical administration. Since both Brash et al, and the treatment of curettage from Voet yielded beneficial results in treating precancerous lesions, one of ordinary skill in the art would have been motivated to make the modifications to combine the references together.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Claims 1, 4-6, 8-15, 35, and 36 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Lou et al as applied to claims 1, 4-5, 8-15, and 35 above, and further in view of An Kathy et al (Cyclooxygenase-2 expression in murine and human nonmelanoma skin cancers: implications for therapeutic approaches, Photochemistry and photobiology, (2002 Jul) Vol. 76, No. 1, pp. 73-80).

The teachings of Lou et al are set forth above and applied as before.

The teachings of Lou et al do not specifically teach treating actinic keratosis in human.

An Kathy et al teach COX-2 expression was also increased in human actinic keratoses.

An Kathy et al also teach acute exposure of the human skin to UVB (minimum erythema dose x 4) caused a transient enhancement of the COX-2 expression, which reverted to baseline within

hours; however, in murine skin the expression persisted for several days. Pretreatment with the topically applied green tea extract (1 mg/cm<sup>2</sup>) largely abrogated the acute COX-2 response to UVB in mice or humans. In summary, enhanced COX-2 expression serves as a marker of epidermal UVB exposure for murine and human NMSC. These results suggest that COX-2 inhibitors could have potent anticarcinogenic effects in UVB-induced skin cancer (see Abstract).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the green tea extract to treat actinic keratoses from An Kathy et al since An Kathy et al teach green tea extract (1 mg/cm<sup>2</sup>) largely abrogated the acute COX-2 response to UVB in mice or humans. Since both Yanaga et al and An Kathy et al teach using green tea extract to treat precancerous lesion, one of ordinary skill in the art would have been motivated to make the modifications and combine the two references together.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Claims 1, 4-6, 8-26, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lou et al as applied to claims 1, 4-5, 8-15, and 35 above, and further in view of Katiyar (Katiyar, Skin photoprotection by green tea: antioxidant and immunomodulatory effects, Current Drug Targets-Immune, Endocrine & Metabolic Disorders, 2003, Sept, 3, 234-242).

The teachings of Lou et al are set forth above and applied as before.

The teachings of Lou et al do not specifically teach using green tea extract to treat precancerous lesion in human, neither do Lou et al teach the claimed amount of the polyphenols mixtures.

Katiyar teaches extensive laboratory data in animals as well as some in human system demonstrate that polyphenols from green tea possess anti-inflammatory, anti-oxidant, immunomodulatory and anti-carcinogenic properties, therefore the supplementation of EGCG or GTP (green tea polyphenols) in skin care products may have profound impact on various human skin disorders. Also the photoprotective potential of green tea polyphenols against UV-induced DNA damage and immune suppression suggest its possible beneficial effects against solar UV light-induced nonmelanoma and melanoma skin cancer incidence. Supplementation of skin care products or sunscreens with polyphenols from green tea may have beneficial photoprotective effects in human systems (page 240, 1<sup>st</sup> column, last paragraph bridging 2<sup>nd</sup> column). Katiyar also teaches the active constituents responsible for therapeutic efficacy in green tea are called epicatechins or epicatechin derivatives. These epicatechins are also commonly called “polyphenols” and are easily soluble in water and organic solvents like acetone, ethanol etc. The major epicatechins found in green tea are (-) epicatechin, (-)epicatechin-3-gallate, (-) epigallocatechin, and (-) epigallocatechin-3-gallate (page 235, 2nd column, 3rd paragraph).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use green tea polyphenols against solar UV light-induced nonmelanoma and melanoma skin cancer incidence in human, as evidenced by Katiyar EGCG and green tea polyphenols are used interchangeably in the art for their photoprotective potentials. Therefore, one of the ordinary skills in the art would have been motivated to use green tea polyphenols

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mixture from Katiyar to treat precancerous lesion in Lou et al. Regarding to the claimed amount of each polyphenol constituent, the concentration of each component may vary according to the growth condition, harvest season, and extraction method of green tea, and the result-effective adjustment in conventional working parameters is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

Since both Lou et al, and Katiyar teach the topical use of green tea components in photocarcinogenesis, one of ordinary skill in the art would have been motivated to combine the references together.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Applicant's arguments have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Lou et al and Katiyar.

## Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Qiuwen Mi whose telephone number is 571-272-5984. The examiner can normally be reached on 8 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Qiuwen Mi/

Examiner, Art Unit 1655